Office Action Summary	Application No.	Applicant(s)	
	10/581,008	TAKAMI ET AL.	
	Examiner	Art Unit	
	STEVEN C. POHNERT	1634	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,9 and 12-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,9 and 12-16* is/are rejected.

7)☒ Claim(s) *5,9 and 12-16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 May 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/27/2008*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *9/26/2009*.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to papers filed on 4/17/2009.

Claims 5, 9, 12-16 are pending.

This action is non-final as it presents new grounds of rejection.

The enablement rejection previously presented has been withdrawn upon further consideration.

Claim Objections

1. Claims 5, 9, 12-16 are objected to because of the following informalities:

Claims 5, 9, 12-16 recite, "phospholipidosis non-inducing compounds." It appears the claims wish the limitation to be drawn to compounds that do not induce phospholipidosis, however the recitation "non-inducing" appears to suggest the compounds have an effect in counteracting phospholipidosis induction, which based on the specification is not the intent. The claims should be amended to reflect the compounds are either known to induce phospholipidosis or known not to induce phospholipidosis.

Claim 15 recites, "wherein the average variation rate is the following formula...." Thus claim 15 appears to be defining the average variation rate. It appears the intent of claim 15 is defining the formula by which the average variation rate is being calculated. If the intent of the claims is to calculate the average variation rate by the formula claim 15 should be amended to recite, "wherein the average variation rate is calculated by the following formula."

Claims 16 is objected to as it recites, " the phospholipidosis is induced in an organ or tissue derived from the mammalian cell being exposed to the compound." The claim appears to be asserting that a tissue or organ is derived from a mammalian cell, however cells are derived from tissue. There is nothing in the specification to suggest that the specification is enabling for taking a cell and deriving a tissue or organ from it as the claim appears to require. This objection can easily be overcome by amending the claim to require that phosholipidosis is induced in a cell derived from a tissue or organ.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 5, 9, 12-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5, 9, 12-16 are indefinite because it lacks a positive active step relating back to the preamble. The preamble recites a method of predicting phospholipidosis induction potential of a test compound, step 1 claims determining a standard for judgment of the presence or absence of phospholipidosis inducing potential while the second step claims detecting expression of a test compound and comparing to the average variation rate. The claim does not present an actual step of predicting a

phospholipidosis induction potential. The claims are unclear as to what the comparing the average variation rate reveals about phsopholipidosis.

Claim 5, 9, 12-16 are indefinite as step 1 (a) is drawn to detecting expression in samples containing a mammalian cell exposed to two or more known phospholipidosis-inducing compounds and two or more known phospholipidosis non-inducing compounds. It is unclear how treating a single cell with 4 different compounds with two different effects results in a standard. The specification provides for treating 4 different cultures of cells with individual compounds and analysis based on such. The applicant should amend the claims and state on the record the intent of the claims.

Claims 5, 9, 12-16 are indefinite as the recite, "an average variation rate capable of correctly judging the presence or absence of the phospholipidosis induction potential of the above mentioned compounds by not less that about 70% based on the relationship between an average expression variation rate of the genes and the phospholipidosis induction potential." It is unclear in the claims presented what the metes and bounds of the relationship encompass. Is there a certain level of reproducibility required between inducing and non-inducing compounds, or between inducing compounds and non-inducing compounds separately. Further, it is unclear if the claim requires that the gene expression of all the compounds on a single cell varies by 70%, 70% of individual compounds have the same variation rate, it the expression of the genes cannot vary less than 70%, or if the inducing compounds must vary less than 70% from each other or if the inducing compounds vary less than 70% from the non-

inducing. The claims should be amended to clearly indicate what is being varied by 70%.

Claims 5, 9 and 12-16 are indefinite as (1)(b) is drawn to using, as a standard value an average variation rate. It step 1(b) is drawn to calculating an average variation rate or using an average variation rate. If the claims are drawn to using an average variation rate it is unclear how it is being used.

Claim 5 recites the limitation "the average variation rate of gene expression with the value obtained by step 1" in 2(b). There is insufficient antecedent basis in step 2 for this limitation in the claim. "average variation rate" is previously recited in the claim in step 1. Thus the claim appears to be comparing the average variation rate of obtained in step 1(b) to itself. Thus the metes and bounds of the claim are unclear. If the intent of the claim is to compare the expression data of step 2 to the standard value of step 1 the claim should be amended to compare the standard of judgment of step 1 to the expression variation of step 1.

Claim 12 recites the limitation "the mammal cell" in the second line. Claim previous recites, "mammalian cell." There is insufficient antecedent basis for this limitation in the claim. This rejection can be easily overcome by amending the claim to recite, "the mammalian cell." Claim 13 is rejection as it depends from 12 and has all the limitations.

Claims 12 and 13 recites the limitations "the phospholipidosis inducing compound" or "the phospholipidosis non-inducing compound" in the second line. There is insufficient antecedent basis for this limitation in the claim. Claim 5 from which claims

12 and 13 depend "recite two or more known phospholipidosis inducing compounds and two or more known phospholipidosis non-inducing compounds." Thus it is unclear the metes and bounds of claims 12 and 13 which are drawn to single compounds, while claim 5 appears to require at least two phospholipidosis inducing compounds or phospholipidosis non-inducing compounds.

Claim 16 recites the limitation "the compound" in the last line. The metes and bounds of the claims are unclear as claim 5 from which it depends recites "phospholipidosis inducing compounds", "non-phospholipidosis inducing compounds" and "test compounds" thus it is unclear to which compound this limitation is referring.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claim 5, 12, 13, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reasor et al (Exp Biol Med (2001) volume 226, pages 825-830) in view of Mendrick (WO02/10453 Published February 7, 2002), Zhou (Current opinion in Drug discovery and Development (2003) volume 6, pages 339-345) as evidenced by Affymetrix blast searches printed 6/29/2009.

The claims are drawn to a method of predicting phospholipidosis by detecting gene expression variation of a set of genes set forth in SEQ ID NO 1, 3, 5, 7, 9, 11, 13, 15 , 17, 19, 21 and 23, by determining expression variation to produce a standard value for comparison by analysis of cells treated with at least two compounds known to induce phospholipidosis and two compounds known not to induce phospholipidosis, then detecting gene expression variation of a test compound and comparing the average variation rate of gene expression with the standard value obtained by use of compounds with known phospholipidosis inducing potential. The claims are drawn to detecting expression variation of the genes of SEQ ID NO 1, 3, 5, 7, 9, 11, 13, 15 , 17, 19, 21 and 23. This can be broadly interpreted to encompass additional sequences as the claims have comprising language and do not clearly indicate detection of expression of only the recited SEQ ID NO.

Reasor teaches that phospholpidosis is a recognized pre-clinical toxicological problem in the pharmaceutical industry (826, 2nd column). Reasor teaches that exposure to phospholipidosis inducing compounds results in the sequestration into lamellar bodies (claim 12). Reasor teach chlorphentermine and amiodarone are phospholipidosis inducing compounds (page 828)(claim 13). Reasor teaches that the use of biomarkers to evaluate damage to cells would be helpful (page 829).

Reasor does not teach predicting phospholipidosis induction potential of a test compound by comparison to a standard value generated from other compounds known to be have toxicological responses or known not to have toxicological responses (claim

5 and 9). Reasor does not teach measuring gene expression of SEQ ID NO 1, 3, 5, 7, 9, 11, 13, 15 , 17, 19, 21 and 23.

However, the specification teaches that Mendrick discloses methods of predicting toxicity of a test compound, which comprises the examining of expression of between 2 to 100 genes selected from an enormous group of genes in the presence of a test compound and comparing the results with average expression amounts of respective genes previously calculated using known positive and negative compounds (page 2, 1st full paragraph).

Mendrick teaches that any available means for monitoring changes in nucleic acid expression may be used for testing toxicological response to compounds (page 20, 1st paragraph and 23, 2nd paragraph). Mendrick teaches the use of gene chips containing two or more genes can be used (page 20, 2nd paragraph). Mendrick teaches a preferred solid support is a high density microarray (page 23). Mendrick teaches the invention utilize array formats that hybridize up to 1,000,00 hybridization events. Mendrick teaches the use of Affymetrix genechip. Mendrick teaches the discriminating genes had a 70% ability to discriminate compounds (page 43)((1b).Mendrick teaches there are numerous methods of modeling toxicity including using each variable and weighting them independently (claim 15). Mendrick teaches use of cells from tissues for assaying toxicity in the tissue.

Attention is directed to MPEP 2129 [R-6], Admissions as Prior Art, which states in part:

I. ADMISSIONS BY APPLICANT CONSTITUTE PRIOR ART

A statement by an applicant >in the specification or made< during prosecution identifying the work of another as "prior art" is an admission **>which can be relied upon for both anticipation and obviousness determinations, regardless of whether the admitted prior art would otherwise qualify as prior art under the statutory categories of 35 U.S.C. 102. Riverwood Int'l Corp. v. R.A. Jones & Co., 324 F.3d 1346, 1354, 66 USPQ2d 1331, 1337 (Fed. Cir. 2003); Constant v. Advanced Micro-Devices Inc., 848 F.2d 1560, 1570, 7 USPQ2d 1057, 1063 (Fed. Cir.1988).

Further Zhou et al teaches HU133A which comprises probes for the detection of SEQ ID NO 1, 3, 5, 7, 9, 11, 13, 15 , 17, 19, 21 and 23 were known. Affymetrix blast searches demonstrates that HU133A gene chip comprised 1, 3, 5, 7, 9, 11, 13, 15 , 17, 19, 21 and 23.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to apply the microarray toxicological method of Mendrick to phospholipidosis involved toxicity as taught by Reasor. The artisan would be motivated to apply the teachings of Mendrick to Reasor because Reasor suggests the use of biomarkers for phospholipidosis inducing compounds, while Mendrick demonstrates the use of nucleic acid expression as biomarkers. The artisan would be motivated to use the Affymetrix Hu-133A array in the toxicological methods as Zhou demonstrates the Hu-l33A array was known and had been used for toxicological analysis, while the Affymetrix blast search demonstrates probes to all the claimed SEQ ID NO were present on the HU-133A chip.

5. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Reasor et al (Exp Biol Med (2001) volume 226, pages 825-830) in view of Mendrick (WO02/10453 Published February 7, 2002), Zhou (Current opinion in Drug discovery and Development (2003) volume 6, pages 339-345) as evidenced by Affymetrix blast

searches printed 6/29/2009 as applied to claim5, 9, 12-13 and 16 above, and further in view of Jan-Peter (EXP Toxic Pathology (2004) volume 55, pages 347-355).

Reasor, Mendrick, Zhou do not teach the use of halpoperidol as a compound that does not induce phospholipidosis.

However, Jan-peter teaches the use of haloperidol as a negative control (page 351).

Therefore it would have been prima facie obvious to one of skill in the art at the time the invention was made to use the specific teaches of Jan-Peter to compounds that were not known to induce phosphoilipidisis in the method the Reasor, Mendrick, Zhou. The artisan would be motivated to look to the art for the teachings of specific compounds which do or do not induce phospholipidosis in view of the teachings of an-Peter. The artisan would have a reasonable expectation of success as the artisan is merely using a specific compound known not to controls for phospholipidosis.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN C. POHNERT whose telephone number is (571)272-3803. The examiner can normally be reached on Monday-Friday 6:30-4:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Steven C Pohnert/
Examiner, Art Unit 1634

Steven Pohnert